Summary CCCEH-EPA Meeting 5/15/13

New Information:

A. Dose Reconstruction: EPA can contact NYC DOH/housing for linked data set CCCEH and NYC housing pesticide application records 1998-2002 [Wendy McKelvey 212.676.2603 wmckelveehealth@nyc.gov]
B. Lead: EPA could ask CCCEH for additional analysis age of housing (Pb surrogate) and CPF to provide evidence for/against association CPF and Pb(housing age)
C. Lead: ND Domains affected differ: V. Rauh stated while Pb and CPF both affect ND – the two compounds affect ND differently. Pb-aggression, impulse control – outward motivated. CPF- working memory, attention, focus – inward processing and organization issues.
D. Lead: Brain Imprint differs: See paper on MRI-Pb exposure compared to Rauh 2012 MRI CPF, illustrate areas of brain affected different. [Cecil et al. 2008]
E. Other: Other items included in EPA list of questions/issues either addressed with published or previously provided information, or authors discussed factors against utility of pursuing SAP motivated analyses.

Main Points:

1. Exposure Information:
    a. EPA can contact NYC DOH/housing for linked data set CCCEH and NYC housing pesticide application records 1998-2002 [Wendy McKelvey 212.676.2603 wmckelveehealth@nyc.gov]
    b. EPA can ask CCCEH for 'greyed out' pesticide product name; unlikely useful (quality)
    c. R. Whyatt did previously performed an analysis assuming highest air concentration and back-calculated (crude) to about 10% the dose level needed to observe ChE inhibition – can send on request
    d. D. Hattis PBPK submitted to Risk Analysis – upon publication, review and ask to speak with Hattis concerning CCCEH exposure data
    e. Whyatt and Bradman paper on pesticide exposure assessment issues – difficulty in obtain pesticide product name from family participants – general information on obtaining pesticide use information
2. Lead:
    a. EPA could ask CCCEH for additional analysis age of housing (Pb surrogate) and CPF to provide evidence for/against association CPF and Pb(housing age)
    b. ND Domains affected differ between CPF and lead: V. Rauh stated while Pb and CPF both affect ND – the two compounds affect ND differently. Pb-aggression, impulse control – outward motivated. CPF- working memory, attention, focus – inward processing and organization issues.
    c. Brain Imprint differs between CPF and Lead: See paper on MRI-Pb exposure compared to Rauh 2012 MRI CPF, illustrate areas of brain affected different. [Cecil et al. 2008]
    d. Authors and group reviewed evidence regarding confounding effect lead:

i. Subtle differences in exact ND outcomes-pb must be causally related to same ND outcome to be a confounding variable in this analysis; prenatal Pb-CPF – not related; Post natal low CPF and postnatal low Pb not related; appears some evidence of effect modification (together different than separate, but both compounds have a statistical effect)

e. Discussed imputing lead levels for "high" CPF group (missing data) – assume non-random missingness – authors stated not advisable due to substantial proportion of lead dataset below LOD (0.5 ug/dL).

3. PAH, other environmental exposure/shift in exposure over time:
    a. Study design did not include repeat measures of exposure; therefore, design does not allow an evaluation of changing exposure over time.
    b. Could do growth curve analysis by converting ND outcomes (Bayley 12, 24, 36 months and IQ, and ADHD, and CBCL) to Z-scores – but unclear value of resulting information (may show inconsistent pattern; dissimilar ND outcomes, would not necessarily expect them to track together).
    c. Figures 1 and 2 in Rauh et al. 2006 reflect individual level data (not aggregate). Thus authors state in many ways this analysis is completed (age 1-3).
    d. V. Rauh states presence of brain effects as shown in MRI studies implies persistent adverse effect of pre-natal CPF exposure (irreversible).
4. Co-Exposures:
    a. Multi-variable models adjusted for major known risk factors (other OP, SES, ND risk factors); authors state available evidence does not indicate strong likelihood of unmeasured confounding variable.
    b. Authors state more research needed in other populations to address comparative risk analysis issue – relative weight of CPF v. Pb with ND – this is "next generation" study building upon initial research.
    c. Authors state data show CPF as well as other compounds play a role- multi-factorial causation of disease (see supplemental tables Rauh 2012 for relative contribution of each factor, beta coefficients).
    d. Authors state sample size too low, and available methods untested to fully analyze mixture effect on CPF in this cohort. They are developing methods in another cohort (N=1600), not pesticide related.
5. Other Issues Raised in External Reviews (SAP 2008, 2012, Federal review 2012):
    a. Statistical Analyses and Data Presentation:
        i. EPA may request analysis to model major OP's in use pre-ban in both categorical and continuous measures to learn about degree of residual confounding, and threshold of effect
            1. Considered low utility due to likely model instability (collinearity)
            2. Authors suggested threshold analysis (spline models) performed in Rauh 2012 superior approach to evaluating threshold effect than SAP suggested approach (suggested 2008, prior to Rauh 2011 publication)
        ii. Methods to extrapolate below LOD and outliers (model diagnostics)

1. See paper Rauh and Arunajadai 2012– these issues addressed

iii. Alternative data presentation idea:

1. Average IQ score by CPF category, test for statistical significance of difference
    a. Authors state this data presentation/analysis less statistically robust and less informative than method published.
2. EPA can request this analysis, however per above, likely low value.

b. Secular change (and not CPF) causes change in health outcomes pre-/post-ban: EPA may request stratified analysis of PAH on Bayley outcomes, before and after 2001 to show no difference by strata. Supporting evidence that indeed CPF and not another coincident secular event that causes difference in CPF before and after (Whyatt et al. 2004, Table 4)

i. Authors state that if this true, would expect to see an effect in early period with other environmental chemicals tested; this is not the case.

ii. What if it does not show what is anticipated, due to statistical anomalies in dataset- then what? Re-consider this request.

iii. This is considered low utility, and was confusing to CCCEH researchers

c. Qualifications of ND test administrators:

i. See meeting transcript 2008 SAP – response to DAS question on this point. Full information provided.